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CERMAK KENEALY VAIDYA & NAKAJIMA LLP
515 E. BRADDOCK RD
ALEXANDRIA, VA 22314

EXAMINER	
HIRIYANNA, KELAGINAMANE T	
ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
11/27/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ACERMAK@CKVNLaw.COM
CGOODE@CKVNLaw.COM
PTADMIN@CKVNLAW.COM

Office Action Summary	Application No.	Applicant(s)	
	10/561,902	SCHULE ET AL.	
	Examiner	Art Unit	
	KELAGINAMANE T. HIRIYANNA	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 September 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6 and 20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 & 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submissions of 09/28/2009 & 07/23/2009 are entered.

Applicant's response filed on 09/28/2009 & 07/23/2009 in response to office action mailed on 01/28/2009 has been acknowledged.

Claims 1 & 5 are amended.

Claim 20 is new.

Claims 1-6 and 20 are pending and are examined in this office action.

Applicants are required to follow Amendment Practice under revised 37 CFR §1.121. The fax phone numbers for the organization where this application or proceeding is assigned is ***571-273-8300.***

Withdrawn: Claims 1-6 rejection under 35 USC 103 (a) as being unpatentable over Lai et al (2002, J. Bone and Mineral Res. Vol.17; supp (1), pp. S129; art of record) in view of Amaar et al (2002, J. Biol. Chem. 277:12503-12059; art of record) in view of Muller et al (2002, The EMBO Journal 21:736-748; art of record) for the reason of record as set forth in the office action mailed on 01/28/2009 is withdrawn in view Applicants amendments to claims and in view of revised 35USC103 rejections below.

Withdrawn: Claims 1-4 rejection under 35 USC 102 (b) as being anticipated by Amaar et al (2002, J. Biol. Chem. 277:12503-12059) for the reason of record as set forth in the office action mailed on 01/28/2009 is withdrawn in view Applicants amendments to claims and in view of revised 35USC103 rejections below.

Withdrawn: Claims 1-5 rejection under 35 USC 102 (b) as being anticipated by Lai et al (2002, J. Bone and Mineral Res. Vol.17; supp (1), pp. S129; art of record) for the reason of record as set forth in the office action mailed on 01/28/2009 is withdrawn in view Applicants amendments to claims and in view of a revised 35USC103 rejections below.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

"The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention."

Claims *1-6 and 20* are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The scope of invention as claimed encompasses promoting the activity (any activity i.e., for example proliferation, metabolic activity, transcriptional activity, translational activity or synthesis of a specific protein, or secretion of specific protein, specific modifications of proteins etc., etc.) of osteoblasts *in vivo* and modulating (both increasing and decreasing) the bone formation rate.

The specification only teaches FHL2 transgene expression that increases cellular FHL2 activity of osteoblasts and/or FHL2/RunX interactions and deposition of ECM.

The application does not disclose measuring any other activities of osteoblasts. Thus the number of representative examples of the broad genus of "the activity of osteoblasts" provided in the specification does not commensurate with the scope and breadth of instant claims.

Applicant is referred to the guidelines for ***Written Description Requirement*** published January 5, 2001 in the Federal Register, Vol.66, No.4, pp.1099-1110 (see <http://www.uspto.gov>). The disclosure of a single species is rarely, if ever, sufficient to describe a broad genus, particularly when the specification fails to describe the features

of that genus, even in passing. In analyzing whether the written description requirement is met for the genus claim, it is first determined whether a representative number of species have been described by their complete structure or feature. Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics.

Since the specification fails to disclose other claimed activities that encompass sufficient number of examples of activities of a tissue specific cell (osteoblast) it is not possible to envision the broadly claimed "the activity" of osteoblast. One cannot describe what one has not conceived. Therefore, the lack of disclosure in the specification is not deemed sufficient to reasonably convey to one skilled in the art that the applicants were in possessions of the huge genera recited in the claims at the time the application was filed. Furthermore the possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with *sufficient relevant identifying characteristics* (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Accordingly one of skill in the art would conclude that applicant was not in possession of the claimed genus because a description of a single member of this genus would not be representative of claimed genus of activities.

Claims 1-6 and 20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of identifying an agent that increases osteoblastic cell FHL2 expression or activity, does not enable modulating (increasing or decreasing) any activity of a osteoblastic cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The scope of invention as claimed encompasses promoting the activity (any activity i.e., for example proliferation, metabolic activity, transcriptional activity, translational activity or synthesis of a specific protein, or secretion of specific protein, specific modifications of proteins etc., etc.) of osteoblasts *in vivo* and modulating (both increasing and decreasing) the bone formation rate. The specification however, only

teaches regarding FHL2 transgene expression that increases cellular FHL2 activity in osteoblasts and consequent increase in FHL2/RunX interactions in an osteoblast.

The specification does not enable measuring any other activity of osteoblast other that that of increasing deposition of extracellular matrix and increasing Fhl2 expression that is further correlated with Runx2-induced transcriptional activity. Applicant does not enable measuring any other activity of the osteoblast

Art at the time of invention art only teaches regarding an increase in Fhl2 activity in an osteoblast is achieved by over expressing an Fhl2 transgene in said osteoblast (Amaar et al., 2002, J. Biol. Chem. 277:12503-12059 and Lai et al., 2002, J. Bone and Mineral Res. Vol.17; supp (1), pp. S129; art of record) and an increase in cell proliferation. An elevation of activities certain enzymes, osteopontin and bone sialoprotein, an upregulation of osteocalcin and bone mineralization along with synergized Cbfa1 (Runx2) and FGF2 activities were also observed in these cells (Lai et al; supra). However, neither the art nor the specification teach regarding enable modulation (both increase and decrease) bone formation by the osteoblast

Since the specification fails to disclose enabling examples any of the broadly activity of the osteoblast including decreasing the bone formation by osteoblast, and does not teach measuing other than an over expression of Fhl2 transgene and increasing Fhl2 protein interaction with cellular Runx2 protein, one of skill in the art would find the applicant's disclosure is not reasonably enabling for the fully claimed scope and would require undue amount of experimentation to practice the invention in its full scope. At issue, under the enablement requirement of 35 U.S.C. 1 12, first paragraph is whether, given the Wands-factors, the experimentation was undue or unreasonable under the circumstances. "Experimentation must not require ingenuity beyond that to be expected of one of ordinary skill in the art." See Fields v. Conover, 443 F.2d 1386, 170 USPQ 276 (CCPA 1970).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. The omitted structural cooperative relationships are: the purpose or the conclusion of the method steps is missing. One of skill in art would not be able to envision the use of the compound identified with the claimed method steps. The claim also requires a commensurate conclusion, so that the Artisan knows what is encompassed, or if more is needed to infringe the claim.

Claims 2-5 and 9 are rejected for depending from rejected base claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-6 and 20 are rejected under 35 USC 103 (a) as being unpatentable over Lai et al (2002, J. Bone and Mineral Res. Vol.17; supp (1), pp. S129; art of record) in view of Marie et al (2002, Histol. Histopathol. 17:877-885), Amaar et al (2002, J. Biol. Chem. 277:12503-12059; art of record) and Muller et al (2002, The EMBO Journal 21:736-748; art of record).

The above claims are directed to a method of selecting a test compound (that modulates FHL2 protein level in a cell) comprising the steps contacting at least one osteoblast in vitro with a test compound and determining the FHL2 protein level, comparing the same with FHL2 protein level in a control osteoblast cell, determining whether the test compound is capable of an action selected from a Markush group including i)promoting the activity of osteoblasts in vivo, ii) modulating the bone formation rate in a non-human test animal, iii) promoting the formation of ECM in a non-human test animal or iv) a combination thereof. In further limitations different ways of estimating Fhl2 protein in a osteoblast, use of different osteoblast cell lines etc.

Regarding the claims 1-5 Lai teaches over expressing FHL2 gene and protein in osteoblasts (MC3T3-E1) in vitro by contacting FHL2 cDNA (a compound) cloned in a expression vector (Abstract). Lai further teaches Fhl2 expression is up regulated in these cells which further show an cell proliferation, matrix mineralization, osteocalcin up regulation and Runx2 (Cbfa1) up regulation. Regarding claim 6 RunX2 is well known in the art, at the time of invention, as a transcriptional factor involved in the expression of osteocalcin. Lai further teaches that FHL2 may play an important role in bone formation in vitro and in vivo. Lai clearly teaches FHL2 up-regulates osteoblast growth and differentiation and potentiates FGF2 activity, which the prior art amply teaches as playing an important role in osteoblast activity and bone formation in vivo. Lai however, does not teach determining the level of interaction between Fhl2 protein and Runx2 protein in the osteoblast.

Marie clearly teaches that FGF2 is an essential factor involved in skeletal development, bone formation and regulates the proliferation of osteoblasts in vivo (entire article; abstract).

Regarding the claims Amaar teaches over expressing FHL2 gene and protein in bone cells (U2 osteoblasts or osteosarcoma cells) in vitro by contacting FHL2 cDNA (a compound) cloned in retroviral expression vector (p.12054, col.2, paragraph 8 bridging p.1205; p.12059, col.1, paragraphs 3-5 bridging col.2). Amaar further teaches that Fhl2 is strongly localized in the nucleus and interacts with IGBF5, an mportant bone formation regulator (abstract; p.12059, col.1, paragraphs 3-5 bridging col.2). Besides this FHL2 has been shown to interact with other proteins involved in transcription regulation in osteoblasts and the presence of multiple lim domains and zinc finger motifs may facilitate these interactions (p.12059, col.1, paragraphs 3-5 bridging col.2).

Muller teaches Fhl2 is transcriptional co-activator and that FHL2 binds and selectively activates the transcriptional activity of androgen receptors (entire article; Abstract; p.746, col.2, 2nd paragraph). Muller further clearly teaches synthetic compounds cellular compounds capable of activating signaling pathway that stimulates FHL2 expression in cells (p.739; p.742 col. 1 bridging col.2).

Thus it would have been obvious to one of skill in the art to identify compounds that modulate FHL2 activity/protein level in a osteoblast cell in vitro system as taught by Lai and further establish the compounds such as FGF2 that modulate Fhl2 expression in vitro are capable of action in vivo, in a subject, in the bone formation or osteoblast activity as taught by Marie and still further try establishing FHl2 interaction with other proteins (such as IGFBP-5, RunX/Cbfa, androgen receptor) involved in the regulation of osteoblst activity and bone formation as taught by Amaar and/or Muller. One of skill in the art would have motivated to try to establish physical interaction between Fhl2 and other transcriptional activators in osteoblast. One of skill in the art would have a reasonable expectation of success in establishing the protein interaction between Fhl2 with other transcriptional activators (such as IGFBP-5, RunX/Cbfa, androgen receptor) in osteoblasts that are involved in bone formation as the art teaches that Fhl2 clearly interacts with several transcriptional activator proteins and further the art teaches the routine methods for determining physical interactions of transcriptional regulators in osteoblasts. Thus the invention was prima facie obvious to the Artisan at the time of invention.

Conclusion

No claim allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Kelaginamane Hiriyanna Ph.D.*, whose telephone number is **(571) 272-3307**. The examiner can normally be reached Monday through Thursday from 9 AM-7PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Joseph Woitach Ph.D.*, may be reached at **(571) 272-0739.** The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). When calling please have your application serial number or patent number, the type of document you

are having an image problem with, the number of pages and the specific nature of the problem. For all other customer support, please call the USPTO call center (UCC) at (800) 786-9199.

/Robert M Kelly/

Primary Examiner, Art Unit 1633